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THE HYDROGEN EXCHANGE OF PHENOL, ITS ETHERS, AND AROMATIC AMINES

WITH LIQUID DBr

- USSR -

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FOREWORD

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WITH LIQUID DBr

Earlier we established the basic laws of deuteron exchange in aro-
matic hydrocarbons dissolved in liquid DBr /1, 2/. In this article we
shall present the results obtained from the study of hydrogen exchange
with liquid DBr in aromatic compounds with substituents containing an
oxygen or nitrogen atom. (The results of this work were presented at the
All-Union Meeting on the Use of Isotopes /3/. The investigation of phe-
nol and its ethers was included in a dissertation by A. V. Vedeneyev at
the Physico-Chemical Institute imeni Karpov, 1955.)

The free pairs of electrons on the oxygen or nitrogen atoms of the
substituent interact with the π-electrons of the aromatic rings. As a
result the electron density of the ortho and para carbon atoms is increased
(the effect of p, π-conjugation; cf. /4/). The attachment of a proton
(deuteron) to the electron pair of a nitrogen or oxygen atom can cause
their transformation to tetra- or tri-valent positive ions. These features
of the particular compounds determine the qualities of their deuteron ex-
change with acids.

Hydrogen exchange in the compounds in which we were interested (with
the exception of $C_6H_5OC_6H_5$) has been studied by a number of authors, but
under conditions different from ours. Small and Wolfenden /5/ estab-
lished that when phenol is heated with D_2O at 100° there is a slow exchange
of hydrogen in the ring. Acids considerably accelerated the exchange.
Ingold et al. /6/ and Koizumi /7/ showed that exchange is of the type
of electrophilic substitution. The ortho and para hydrogen atoms partici-
pate in the exchange /8/. The same hydrogen atoms are rapidly exchanged
with gaseous DCl /9/. A. I. Brodskiy and G. P. Miklukhin and collabora-
tors /10/ investigated in detail the bimolecular exchange reaction be-
tween the hydroxy group and the phenol ring.

Deuteron exchange in anisole with aqueous DCl is slow, while it is
more rapid with D_2SO_4 /6/ and with glacial acetic acid (with sulfuric-
acid catalysis) /11/. It was possible to substitute three H atoms in
the ring. Exchange of the ortho and para H atoms in the rings of dimethyl
anilin and anilin in aqueous DCl and D_2SO_4 is more rapid than in phenol
/6, 8/.

Kharasch and Brown /12/ have shown that the ortho and para H
atoms of triphenylamine, diphenylamine, and dimethyl analin are exchanged
with C_2H_5OD with D_2SO_4 catalysis in 100 hours at 100°.

EXPERIMENTAL

The equipment for producing liquid DBr and the method of conducting experiments on deuteron exchange have been described earlier $\underline{/13\underline{7}}$. Exchange experiments were usually conducted at 20-25°. The number of hydrogen atoms **n** in the aromatic compounds exchanged with deuterium with a deuterium content in HBr no less than 5 atom-% was computed from formula (10) (cf. $\underline{/14\underline{7}}$), and at a concentration greater than 80 atom-% from the following formula: $n = \dfrac{c_B N}{c_p^0}$ (1), where c is the concentration of

D in atom-% in the water in which the substance was heated and c_p^0 in hydrogen bromide; N is the number of hydrogen atoms in the substance. Experiments on reverse exchange were computed from formula (11) (cf. $\underline{/14\underline{7}}$). Here c was determined by the drop method with a precision of 0.02-0.05 atom-%. At high D concentrations the water in which the substance was heated was diluted by weight with water of normal isotope composition. All the substances under study were carefully purified and dried before the experiments. The weights of the substances were usually around 0.2-1.0 grams, and of the solvent 15-20 grams.

Preparations. Phenol, ch. d. a. $\underline{/unidentified\underline{7}}$ was distilled twice in vacuo in a stream of dry nitrogen. The second distillation was performed over dehydrated $CuSO_4$, and had a melting point of 40.5-41°. "Pure" anisole was fractionated in vacuo and dried over metallic sodium; melting point 153.5°, n_D^{20} 1.5170. The dimethyl analin was distilled with water vapor, frozen, dried over metallic sodium, and distilled in vacuo; m.p. 192.5°, n_D^{20} 1.5583. The diphenylamine and triphenylamine were distilled in vacuo; m.p., 53.5 and 126.5°, respectively.

All the substances are easily soluble in liquid DBr, form colorless solutions, and can be isolated from solution in unchanged form. This latter was demonstrated by determination of constants after the exchange experiments. The phenol solution turned crimson after 24 hours, and then violet. The same thing happened in 17 hours with the anisole solution. When the duration of the experiments with phenol was increased the quantity of substance isolated diminished. In experiments lasting more than 150 hours no phenol could be isolated. The anisole was still less stable. In 17 hours the anisole turned into phenol. The reaction apparently followed the equation $C_6H_5OCH_3 + HBr \longrightarrow C_6H_5OH + CH_3Br$. The phenol was identified in the form of tribromophenol.

In order to stop deuteron exchange sealed glass rods were dropped into liquid air. Then the DBr was driven off. The remaining substances were extracted with ether. In the case of dimethyl analin and diphenylamine, which form the corresponding hydrobromide salts, an aqueous solution of alkaline was previously added. Then the ether extracts were dried with potash (phenol, diphenylamine, dimethyl anilin) and the ether driven off. In the experiments with diphenylamine, in order to remove the deuterium in the NH-group the ether extract was shaken several times with

water of normal isotope composition. After evaporation of the ether the substances were distilled twice in vacuo (anisole, diphenyl ether, and dimethyl anilin over metallic sodium). After this treatment the substances' constants did not change. Even the first experiments with phenol, anisole, diphenyl ether, and triphenylamine showed that hydrogen exchange with DBr is very rapid. Consequently the equilibrium of the exchange reaction must occur even during the evaporation of liquid DBr, i.e., at a temperature approximately equal to -60° $\boxed{14}$. The value of the coefficient of distribution, which must be known to calculate the number of hydrogen atoms exchanged according to formula (10) (cf. $\boxed{14}$), is known only approximately ($c_f \sim -5$) $\boxed{15}$. Therefore exchange experiments with C_6H_5OH, $C_6H_5OCH_3$, $(C_6H_5)_2O$, and $(C_6H_5)_3N$ had to be conducted with DBr containing 80-100 atom-% D. In this case n can be computed approximately from formula (1).

In the tables presented below the following symbols are used: T = duration of experiment; t° = temperature; m_B = number of moles of substance; m_p = number of moles of solvent; m_{AlBr_3} = number of moles of catalyst $AlBr_3$; c_p° = concentration of deuterium in solvent at beginning of experiment in atom-%; c_B = deuterium concentration in water in which substance was heated, at end of experiment; n = number of deuterium (protium) atoms exchanged; k = rate constant of the hydrogen-exchange reaction computed from a first-order equation.

Hydrogen exchange in phenol (Table 1). Four hydrogen atoms in phenol are exchanged very rapidly with deuterium. One of these belongs to the hydroxyl group and three deuterium atoms enter the ortho and para positions of the ring. This was shown in two ways. Firstly, the phenol, after deuteronization, was brominated to 2,4,6-tribromophenol, and the deuterium from the hydroxy group was washed out with water of normal isotope composition. The water obtained from consumption of the tribromophenol was almost free of deuterium. Second, heating the phenol with heavy water in the presence of alkali yielded 2,4,6-trideuterophenol $\boxed{6}$. Then reverse exchange with HBr was performed with this preparation.

As Table 2 shows, after this only a small quantity of deuterium remained in the phenol (c_B, computed). This corresponded to the relative quantities of substance and solvent taking into account the coefficient of distribution of deuterium α between the C-H and H-Br bonds. (As the data of Table 1 show, in all experiments with phenol a value of n < 3 was obtained for H-exchange in the ring. The reason for this is not clear.)

Hydrogen exchange in anisole (Table 1). The three hydrogen atoms in the ortho and para positions of the ring are exchanged very rapidly. This was shown as follows. 2,4,6-trideuterophenol, obtained by a method described above, was methylated with dimethyl sulfate. Then the 2,4,6-trideuteroanisol was treated with liquid HBr. The results (Table 2) show that the ortho and para atoms engage in exchange.

Experiments were conducted to determine the effect of $AlBr_3$ on the rate of hydrogen exchange. It is well-known that $AlBr_3$ sharply increases the acidity of solutions in liquid DBr. As the data of Table 1 show (experiments 12, 13) the presence of $AlBr_3$ causes a supplementary exchange of more than three atoms (apparently in the meta positions). Unfortunately, in the presence of $AlBr_3$ anisole undergoes an irreversible change within one hour and can no longer be isolated. In an analogous experiment with phenol this latter substance could not be isolated after only 5 minutes with $AlBr_3$.

Hydrogen exchange in diphenyl ether (Table 1). Six hydrogen atoms are exchanged very rapidly. It is natural to assume that these are the hydrogen atoms in the ortho and para positions. In order to check this assumption we obtained decadeuterodiphenyl ether by exhaustive deuteronization of diphenyl ether in a solution of potassium amide in liquid ND_3. When we performed reverse exchange of the decadeutrodiphenyl ether in liquid HBr (Table 2) in ether there remained only a quantity of deterium corresponding to four deuterium atoms remaining in the meta positions of the ring. More than six hydrogen atoms could not be exchanged with liquid DBr even in an experiment lasting 300 hours. But when the acidity of the solution was increased by adding $AlBr_3$ all ten hydrogen atoms could be exchanged in only 3 hours. Thus the meta atoms engaged in exchange.

Hydrogen exchange in triphenylamine, diphenylamine, and dimethyl anilin (Table 3). Nine hydrogen atoms engage in exchange within 5 minutes. No further exchange was observed even after 200 hours. When $AlBr_3$ was added the rate of hydrogen exchange dropped sharply (Table 3, experiments 5-7). In 5 minutes instead of nine, less than one hydrogen atom is exchanged.

Hydrogen exchange is considerably slower in diphenylamine than in triphenylamine. Six hydrogen atoms were exchanged only after 1,000 hours. The addition of $AlBr_3$ had no particular effect on the rate of hydrogen exchange (Experiment 9).

Hydrogen exchange in dimethyl anilin was essentially lacking in experiments lasting more than 1,100 hours. The presence of $AlBr_3$ had no effect on the rate of deuteron exchange (Experiment 17).

EVALUATION OF RESULTS

Deuteron exchange occurs in similar fashion in phenol and its ethers. Hydrogen atoms in the ortho and para positions of the ring exchange very rapidly, while further exchange is not observed even over a long period. Such rapid exchange of nuclear hydrogen atoms is clearly due to the fact that in the ortho para positions the electron density is increased by the effect of p, π-conjugation. In the terminology of A. N. Nesmeyanov [4], there is a transfer of the reactive center from the oxygen atom to the carbon atoms of the ring in the ortho and para positions. The amount by which the rate of the exchange reaction is increased as a result of p, π-conjugation can be seen by comparing the rate of hydrogen exchange of phenol, anisole, and diphenyl ether with the corresponding hydrocarbons. In benzene, exchange is extremely slow ($k_{200} = 5 \cdot 10^{-8}$ sec^{-1} [1]). In toluene and in diphenyl the exchange of para and ortho atoms is much more rapid ($k_{250} = 10^{-4}$-10^{-5} sec^{-1}) [1, 2].

The degree to which the rate of hydrogen exchange depends on the acidity of the deuterizing agent can be seen from the fact that when phenol is heated with heavy water for 400 hours at 100° only two nuclear hydrogen atoms are exchanged [5], while anisole does not enter the exchange reaction at all with heavy water.

Hydrogen exchange between aromatic amines and liquid DBr is quite different from that of phenol and its ethers. In triphenylamine nine atoms are exchanged extraordinarily rapidly. At the same time deuteron exchange was lacking in dimethyl anilin even in experiments lasting more than 1,100 hours. Diphenylamine, in which six hydrogen atoms are exchanged very slowly, occupies an intermediate position.

According to Kharasch [12], in C_2H_5OD catalyzed with D_2SO_4 (at 100° and an acid concentration of 0.6-normal) the hydrogen atoms in the ortho and para positions can be exchanged in all three above-mentioned amines.

The different behavior of the aromatic amines in hydrogen exchange with liquid DBr should be ascribed to their different basicity. It is well-known that their basicity falls in the series: dimethyl anilin > diphenylamine > triphenylamine. If dimethyl anilin forms a very stable salt with liquid DBr, triphenylamine forms no salt at all with DBr. Diphenylamine occupies an intermediate position.

When dimethyl anilin is dissolved in liquid DBr the deuteron is attached to the free pair of p-electrons of the nitrogen atom, which then becomes tetravalent and positively charged. The conjugation of the p-electrons with the π-electrons is broken, and the hydrogen atoms in the ortho and para positions cease to be negative. Therefore the deuteron cannot attach to them, which is a necessary condition for hydrogen exchange in an acid medium. The lack of exchange in dimethyl anilin can also be explained by the fact that the substance is transformed into a positively charged ion, so that the attachment of the deuteron is made more difficult.

In triphenylamine, on the other hand, where no salt is formed, the effect of p, π-conjugation is fully felt, and exchange with DBr, a strong acid, is very fast. Although diphenylamine forms a salt with the acid, the effect of p, π-conjugation is still noticeable, since there is a slow deuteron exchange of hydrogen atoms in the ortho and para positions. The result shows that acid-base interaction does not necessarily lead to complete shift of the proton (deuteron) from the acid to the base $\underline{/}$16$\underline{/}$.

It was interesting to find whether, by a still greater increase in the acidity of the solution, the effect of p, π-conjugation could be eliminated in triphenylamine as it was in dimethyl anilin. It was found that $AlBr_3$ sharply drops the rate of hydrogen exchange in triphenylamine. When stochiometric quantities of $AlBr_3$ are added to triphenylamine, instead of nine less than one hydrogen atom is exchanged in 5 minutes. Apparently the addition of $AlBr_3$ so strongly increases the acidity of the medium that the deuteron is attached to the free pair of p-electrons of the nitrogen atom with the formation of a salt $(C_6H_5)_3 ND^+ AlBr_4^-$. It is also clear that $AlBr_3$ coordinates with the nitrogen atom. A. V. Topchiyev $\underline{/}$17$\underline{/}$ observed that when BF_3 attaches to the nitrogen atom of anilin during nitration of the latter there is a sharp drop in the output of ortho and para isomers. As Table 3 (Experiment 7) shows, if $AlBr_3$ is added in less than equimolar quantity the rate of exchange is higher. This result is quite understandable since only part of the triphenylamine molecule forms a salt (or coordinates with $AlBr_3$).

The addition of $AlBr_3$ to diphenyl ether and anisole not only did not decrease, but even increased, the rate of hydrogen exchange. This indicates that neither the formation of the corresponding oxonium salt nor the coordination of $AlBr_3$ with oxygen atoms occurred.

The difference in behavior of phenol and its ethers on the one hand, and aromatic amines on the other, in hydrogen exchange is explained by the difference in coordinating capacity, and by the different relationship to the proton of the oxygen and nitrogen atoms. It is sufficient to note that in aqueous solution phenol is a weak acid, while aniline is a weak base.

CONCLUSIONS

1. A study was made of hydrogen exchange in phenol and its ethers ($C_6H_5OCH_3$, $C_6H_5OC_6H_5$) and in aromatic amines ($C_6H_5N(CH_3)_2$, $(C_6H_5)_2NH$, $(C_6H_5)_3N$ with liquid DBr, and also with DBr $\neq$ AlBr$_3$ at 25°.

2. In all the compounds of the first group the ortho and para hydrogen atoms exchange immediately, while in the second group of substances rapid exchange is observed only in $(C_6H_5)_3N$, while in $(C_6H_5)_2NH$ these atoms exchange very slowly, and in $C_6H_5N(CH_3)_2$ no exchange is observed even after 1,000 hours. AlBr$_3$ causes exchange of meta atoms in phenol ethers and slows down the rate of the exchange reaction in $(C_6H_5)_3N$.

3. The features of deuteron exchange in aromatic compounds with substituents containing an oxygen or nitrogen atom are explained by the effect of p, π-conjugation. Differences in the behavior of oxygen- and nitrogen-containing substances in hydrogen exchange with liquid DBr and with DBr $\neq$ AlBr$_3$ depend on the difference in their relation to the proton and differences in the coordinating capacity of oxygen and nitrogen atoms.

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Table 1

Isotope exchange of hydrogen in phenol, anisole, and diphenyl ether.

Experiment Number	T	t^o	c_p^o	c_B	n	$\dfrac{m_{AlBr_3}}{m_B}$
			Phenol			
1	10 min.	Room	91.0	53.0	3.5	
2	30 "	25	91.0	55.1	3.6	
3	3 hours	25	91.0	53.1	3.5	
4	27 "	Room	91.0	55.0	3.6	
5	72 "	"	88.8	37.3	2.5*	
6	150 "	"	88.8	39.0	2.6*	
			Anisole			
7	5 min.	Room	93.7	32.9	2.8	
8	10 "	"	90.9	35.1	3.1	
9	30 "	25	90.9	33.8	3.0	
10	3 hours	25	93.7	33.9	2.9	
11	6 "	25	93.7	31.2	2.7	
12	5 min.	Room	83.5	42.0	4.0	0.9
13	30 "	25	93.7	43.6	3.7	0.8
			Diphenyl ether			
14	10 "	Room	90.9	55.0	6.0	
15	3 hours	25	90.9	55.0	6.0	
16	24 "	Room	88.8	54.3	6.1	
17	26 "	"	90.9	55.9	6.1	
18	150 "	"	88.8	51.8	5.8	
19	313 "	"	93.7	57.3	6.1	
20	1 "	25	100	83.4	8.3	1.3
21	1 "	25	100	90.9	9.0	0.5
22	3 "	25	100	95.4	9.5	1.0

* Deuterium from the hydroxyl group was washed out with water of normal isotope composition.

Table 2

Experiments with reverse exchange with liquid HBr at 25°.

Experiment Number	T (min.)	$\dfrac{m_p}{m_B}$	c_B^o	c_B	c_B^* (calculated)
		2,4,6-D-phenol			
1	5	50	3.23	1.04	0.7
2	5	48	3.23	1.22	0.8
3	30	32	3.23	1.14	0.9
		2,4,6-D-anisole			
4	5	80	2.27	0.55	0.55
5	5	59	2.27	0.65	0.63
6	30	38	2.27	0.77	0.77
		Decadeuterophenyl ether			
7	10	150	8.84	4.32	4.64
8	10	230	8.84	4.15	4.24

* c_B (calculated) is the calculated concentration of deuterium after the experiment in the water in which the substance was heated. The number of exchangeable atoms was taken as 3 for phenol and anisole, and 6 for diphenyl ether, while the coefficient of distribution $q = 5$.

Table 3

Isotope exchange in triphenylamine, diphenylamine, and dimethyl anilin.

Experiment Number	T	t^o	$\dfrac{m_p}{m_B}$	$\dfrac{m_{AlBr_3}}{m_B}$	c^o_p	c_B	n
Triphenylamine							
1	5 min.	Room			83.5	48.8	8.8
2	2 hours	25			88.8	51.2	8.7
3	2 "	25			83.9	47.5	8.5
4	200 "	Room			93.7	52.5	8.4
5	5 min.	"		1.2	93.7	3.1	0.5
6	5 "	"		1.0	100	2.6	0.4
7	5 "	"		0.4	100	27.4	4.1
Diphenylamine							
8	1 hour	25	100		5.4	0.2	0.1
9	1 "	25	140	0.5	5.4	0.2	0.1
10	2 "	25	90		88.8	2.6	0.3
11	24 "	Room	140		9.0	2.0	1.1
12	97 "	"	140		9.0	6.6	3.9
13	120 "	"	74		4.4	4.0	5.2
14	696 "	"	59		4.4	4.7	5.6
15	1152 "	"	110		4.4	5.3	6.0
Dimethyl anilin							
16	1 hour	25	50		5.4	0.1	~0
17	1 "	25	51	0.3	5.4	0.1	~0
18	696 "	Room	91		4.4	0.1	~0
19	1152 "	"	97		4.4	0.1	~0
20	1152 "	"	63		4.4	0.02	~0

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